

Resumen por el autor, Franklin P. Reagan.
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Sobre el desarrollo de las venas azigos del cerdo en un periodo
avanzado de la vida embrionaria.

El principal sistema de drenaje intercostal del cerdo está formado, en pleno desarrollo, por las venas hemiazigos y azigos, que se reúnen entre sí para verterse en el conducto de Cuvier izquierdo, y por las venas intercostales superiores derecha e izquierda, que están colocadas por encima de aquellos segmentos cuyo drenaje es generalmente vertebral. Todas estas venas son "ascendentes." Una vena hemiazigos típica se deriva de la postcardinal izquierda en el espacio ocupado por tres a cinco segmentos, situados debajo del límite distal del conducto de Cuvier izquierdo; su porción inferior procede de los segmentos supracardinales. Cuando existe una vena azigos, dos de sus segmentos más superiores pueden proceder de la postcardinal derecha. A consecuencia de las diferencias de nivel de los conductos de Cuvier, mientras que los esbozos intercostales superiores del lado izquierdo siempre comunican con la precardinal muy por encima del conducto izquierdo, los vasos correspondientes del lado derecho pueden verterse en la postcardinal, la precardinal o en el punto en que se reúnen ambas. Cuando comunican con la postcardinal derecha esta vena puede estar casi completamente degenerada en el estado de embrión de 45 mm; cuando vierten en la precardinal derecha la postcardinal izquierda puede persistir en su porción superior hasta el estado de 60 mm. Los troncos del simpático pueden desempeñar un papel importante en el aislamiento de las venas intercostales superiores. La opinión referente al origen de las porciones inferiores de los vasos azigos a expensas de las postcardinales (Hochstetter) es incorrecta. La idea de que en el cerdo las postcardinales no toman parte en el desarrollo general de las venas azigos (Sabin) es también incorrecta.

ON THE LATER DEVELOPMENT OF THE AZYGOS VEINS OF SWINE

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SIXTEEN FIGURES

In the study of the development of azygos veins the main problem involved has been that of the extent to which these veins represent persisting postcardinals. The researches of Zumstein (1), Parker and Tozier (2), McClure (3), Huntington and McClure (4), and Kampmeier (5) have shown that, with the exception of the upper part of the postcardinal and its continuation, the duct of Cuvier, which enter into the formation of the azygos (or of its homologue, the hemiazygos), this latter vessel is derived from anastomoses in a dorsal venous drainage emptying into the postcardinal. The work of Sabin (6, 7), has led to a conclusion that the postcardinals take no part whatever in the formation of azygos or of hemiazygos. Despite these important contributions, our modern text-books continue to exhibit the old and familiar diagrams by Hochstetter in which azygos and hemiazygos are shown as transformed postcardinals.

In 1914 Sabin (6) stated that an oblique vessel (previously described by Kampmeier as a vessel running between the supra-cardinals approximately in the path of the future thoracic duct) is the fundament of a vessel which persists on the right side in such a manner as to correspond to the accessory hemiazygos on the left; that this vessel does not degenerate in a fashion described by Kampmeier, but that it becomes even "larger than the accessory hemiazygos." A study of advanced fetuses and of adults (figs. 11 to 15) has failed to reveal to me structures of any importance corresponding to the vessel running superiorly from right to left in Sabin's figure 17 (7), or vertically as in figure 18 (7). An azygos tributary anastomosing with the

oesophageal drainage can often be found in a position apparently corresponding to the vertically coursing 'oblique vein' in the figure just mentioned; this, however, is not in the direction of the course of the thoracic duct. It is of interest to note that embryos of the bat are devoid of oblique intersupracardinal veins.

In the adult pig, the right superior derivatives of the supracardinal drainage are represented in the inner thoracic wall by the right superior intercostal. This vein has no relation whatever to the azygos as far as direct physical continuity is concerned. Its early relationship will be considered presently. The right superior intercostal drains into the common trunk of the deep cervical and posterior vertebral veins. This right venous trunk empties into the superior vena cava at a point which may be superior to, or at the exact place at which the embryonic postcardinal has joined the precardinal. Occasionally the proximal portion of this venous trunk is a small part of the superior termination of the postcardinal. Without daring to hope that the terminology I propose will be accepted, I shall call this common trunk of the deep cervical, the posterior vertebral, and the superior intercostal, by the name cervicothoracic vein (*vena cervico-thoracalis*). It has no homologue in human anatomy and no satisfactory nomenclature in comparative anatomy. The name would seem to be appropriate, for the reason that the vein drains regions comparable to those drained by the deep cervical, the posterior vertebral, and the superior intercostal of human anatomy. The term attached to any single tributary of this vein would be inapplicable to the common trunk. The order of allusion to cervical and thoracic regions is conditioned by the circumstance that the most immediate region draining into it is the thoracic. In case of the upper inferiorly directed drainage, the blood passes from the cervical to the thoracic region.

In the literature it is possible to find the common stem of all or of any number or combination of the following veins described in various terminologies: *mediastini anterior*, *cervicalis profunda*, *transversa colli*, *intercostalis suprema*, and *vertebrales* of various descriptions. Their common stem is sometimes called

cervicalis profunda despite the fact that the cervicalis profunda in other forms may not be associated with any or quite all of these other veins. While the terminology which I have suggested is perhaps not all that could be desired, it cannot possibly increase the confusion of terminology already applied to this region. The term posterior vertebral vein, as I have employed it, is comparable to the term deep superior intercostal of some authors. It may be objected that this vein lies too far lateral to the vertebrae for the term to be appropriate. Be this as it may, the usage is equally good as that in which the anlagen of the superior intercostal veins proper are described as prevertebral veins. To the vein which I have called cervicothoracic the following terms have been applied by various writers: costocervical, costovertebral, vertebral, and deep cervical.

The cervicothoracic vein and its tributaries arise as supracardinal tributaries to the cardinal system. In the present state of the endothelium question, it is futile to state that they arise from aortic ramifications. Their places of origin are constant with reference to body segments. On either side of the body the supracardinal tributary of the second thoracic interspace develops into the cervicothoracic trunk (figs. 2 to 7). It is generally true that in early stages the drainage of the deep cervical into the cervicothoracic is greater through the first thoracic interspace than through the second. As development progresses, this drainage becomes confined primarily to the second. This is shown diagrammatically in figures 2 to 7. Superiorly, it receives the deep cervical drainage, together with numerous smaller veins; inferiorly, it receives the superior intercostal and the posterior vertebral. After draining the third and often the fourth interspace, the superior intercostal is continued mesially from a strong second-interspace-anastomosis with the posterior vertebral vein. In later development this anastomosis is relatively large, and is so directed as to appear to be the real upper continuation of the posterior vertebral into the cervicothoracic. On neither side is there an 'accessory' drainage comparable to the accessory hemiazygos of human anatomy. The posterior vertebral vein of the adult takes care of a great deal

Fig. 2 is a diagrammatic representation of conditions actually observed in a 24-mm. embryo in which the uppermost supracardinal tributaries enter the cardinal system exactly at the cardinocuvierian junction. The view is latero-ventral. The embryo was injected, cleared after the method of Spalteholz, and then dissected.

Fig. 3 is of the right side of an embryo from the same uterus from which the embryo for the preceding figure was taken. Here the supracardinal enters the postcardinal well below the cardinocuvierian junction.

Fig. 4 is from the right side of a 21-mm. embryo, somewhat more highly magnified than were the two preceding embryos. The supracardinal tributaries enter the precardinal well above the cardinocuvierian junction, having only very slender communications with the postcardinal.

Fig. 5 from the right side of a 50-mm. embryo, showing conditions which in all probability have resulted from antecedent conditions similar to those in figure 2. The postcardinal has become very slender.

Fig. 6 shows the upper azygos and superior intercostal drainage of a 45-mm. embryo; such conditions have probably resulted from those similar to those in figure 3.

Fig. 7 shows conditions in a 59-mm. embryo; these may well have resulted from conditions similar to those shown in figure 4. The right postcardinal is still functioning strongly, having remained free from supracardinal tapping. From figures 5, 6, and 7, it would seem that the level at which the upper supracardinal tributaries enter the cardinal system helps to determine the length of time the superior part of the right postcardinal will function, and also the angle at which the right cervicothoracic will enter the superior vena cava.

Fig. 8 is taken from the left side of a 21-mm. embryo, showing the level at which the left superior supracardinal tributaries enter the precardinal, owing to a constantly low cardinocuvierian junction. It also shows the level at which the postcardinal has received the inferior supracardinal tributary.

Fig. 9 is from the left side of a 75-mm. embryo, showing the resolution of deep cervical, posterior vertebral, and superior intercostal veins out of the superior supracardinals, and also the degeneration of the left precardinal.

Fig. 10 is a ventrolateral view of the right postcardinal of a 24-mm. embryo, showing the point of entrance of inferior supracardinal into postcardinal.

ABBREVIATIONS

A., azygos vein
A.I., intercostal artery (aortic branch)
A.Si., superior intercostal artery
C.t., cervicothoracic vein
D.C., duct of Cuvier
D.Ce., deep cervical vein
Ha., hemiazygos vein
Pc., postcardinal vein
Prc., precardinal vein
P.v., internal vertebral plexus
S., sympathetic trunk

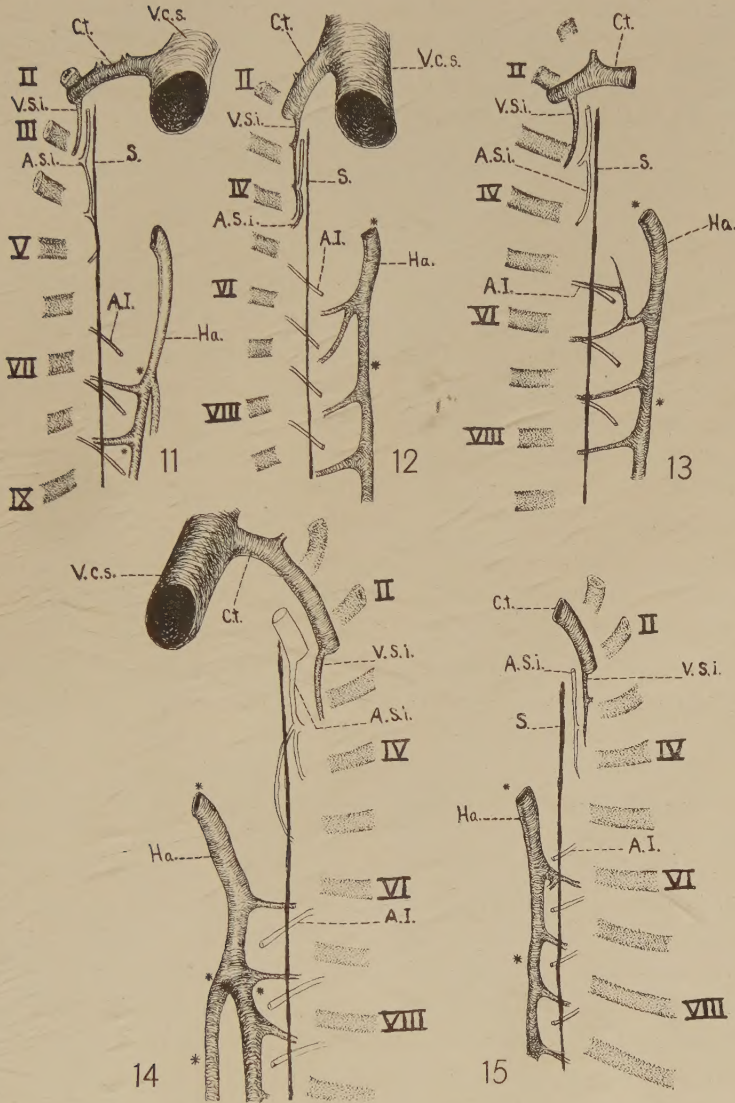
Sc. and Supc., supracardinal veins (respectively superior and inferior).
Si., superior intercostal vein
V.a., azygos vein
V.c.p., deep cervical vein
V.c.s., superior vena cava
V.Ha., hemiazygos vein
V.i., intercostal vein
V.i.s., superior intercostal vein
V.P.v., posterior vertebral vein
W.B., Wolffian body

of the upper intercostal drainage; the superior intercostal drainage of the fourth thoracic interspace is rather meager and often absent (figs. 11 to 15). In the inferiorly adjacent interspace, tributaries respectively of the superior intercostal, and azygos (or hemiazygos as the case may be) are usually lacking or only very weakly developed (figs. 11 to 15). Thus it is that superior intercostals are not in continuity with azygos and hemiazygos. The direction of flow in them is cephalad on both sides.

The relationships of the supracardinal derivatives to the thoracic sympathetic nerve-trunks is of great interest. As previous authors (4 and 5) have shown, the greater portion of the supracardinal tributaries lie mesial to the sympathetic trunks. In most forms this is true of all those tributaries to the postcardinal (the postcardinal lies ventral and somewhat lateral to the sympathetic trunk). At any rate, the most superior supracardinal tributaries to the cardinal system (in most forms, to the precardinals on both sides) lie lateral to the sympathetic trunks. It is perhaps needless to state that these conditions involve a crossing of sympathetic trunk and supracardinal line (figs. 11 to 15). Whatever embryonic connection there may have been between the azygos or hemiazygos and the respective superior intercostal is always absent in the adult pig in the segment where this crossing has taken place (see the fifth thoracic interspace in figs. 11 to 15). The sympathetic trunk is usually applied so closely to the proximal portion of the fifth rib that a communication of azygos and superior intercostal would be obliterated beneath it. Occasionally a small part of the superior intercostal artery may be found under the sympathetic trunk (figs. 11 and 14).

Whereas there may be an absence of superior intercostal or azygos-intercostal veins in certain thoracic interspaces, intercostal arteries are always present either as branches of the superior intercostal artery or of the systemic aorta (figs. 11 to 15).

Sabin has summarized the permanent conditions in the pig as follows (7, p. 29):



Figs. 11, 12, and 13 represent right-lateral views of the azygos, hemiazygos, and superior intercostal veins, showing possible variations in the adult. The specimens were injected with colored gelatin. The figures are, respectively, from gross dissections nos. 2436, 2438, and 2437 of the Princeton Collection. Postcardinal persistence is indicated by asterisks.

Figs. 14 and 15 represent left-lateral views of the hemiazygos and superior intercostal veins. Princeton Collection, nos. 2436 and 2438.

may enter the postcardinal just as it unites with the precardinal to form the duct of Cuvier; second, they may enter the postcardinal inferior (figs. 3 and 6) to its union with the postcardinal; third, they may enter the precardinal above its union with postcardinal (figs. 4 and 7). These are the possibilities for the right side. The third permutation is most seldom encountered. Depending on the level at which these supracardinal derivatives enter the right cardinal system, the main upper part of the postcardinal has a short or a protracted existence. For instance, the entire right postcardinal between the fifth or seventh and the first thoracic interspace may degenerate by the time the embryo is 43 mm. long if the upper supracardinals have entered the postcardinal below the cardinocuvierian junction or near its level. In such a case the last remnant of the upper part of the postcardinal as such will be seen as a frayed-out appendage of the mesial side of the superior intercostal, or of the inferior side of the cervicothoracic. The lower the original point at which the postcardinal has received these supracardinal derivatives, the more distal from the superior vena cava will be the scene of its final disappearance. There is sufficient early variation in the relation of right supra- and postcardinals that a shifting of the later apparent 'attachment' of postcardinal to cervicothoracic or to superior intercostal need not be postulated, though an actual shifting might take place. Tapping of the degenerating postcardinal by the adjacent superior intercostal contributes to its degeneration. The degenerating vessel is being drained below indirectly into the hemiazygos, above into the cervico thoracalis (and possibly the superior intercostal), and laterally into the superior intercostal and mesially into the oesophageal. It is easy to see (fig. 6) that this would lead to speedy degeneration. When the vena cervicothoracalis drains into the precardinal, however, the postcardinal may persist until relatively late (fig. 7). In such a case the postcardinal is seen joining the duct of Cuvier well below the point where the upper supracardinal drainage has tapped. In this case a great deal of blood from the lower part of the postcardinal flows superiorly in that vessel into the duct of Cuvier, preserving the postcardinal merely by usage.

I have found one such case (an embryo of 67 mm.) in which the right postcardinal has become the permanent azygos, the upper part of the left postcardinal and left duct of Cuvier having completely disappeared. On the right side of this embryo all the normal supracardinal derivatives are present. Very clearly, this azygos in a great deal of its extent is a persistent postcardinal. The right superior intercostal is entirely normal; the hemiazygos is practically absent. In another embryo from this same uterus the right postcardinal had persisted, but a left duct of Cuvier was present.

This variation of entrance of the right cervicothoracic into the cardinal vessels is conditioned almost entirely by the variability of cardinocuvierian junction. A high junction causes a low tapping of the supracardinal drainage into the cardinal system; the converse of this is true.

On the left side the anlagen of the cervicothoracic tributaries drain segments of the same level as do those on the right. The great difference in the two sides lies in the relatively low union of pre- and postcardinal veins. Instead of being found in the region of the first or second thoracic interspace, as in case of the right side, the left cardinocuvierian junction is found in the region of the fourth or fifth thoracic interspace. Thus it is that the left cervicothoracic enters the precardinal relatively far superiorly, yet there is not the slightest doubt that these upper supracardinal tributaries are homologous with the right cervicothoracic and its tributaries. For a short time these vessels on the left have a small drainage into the upper portion of the postcardinal. This is severed after a time, leaving the postcardinal essentially as it was (figs. 8 to 9). In case of both sides of the pig, there is constantly a region of from two to four interspaces in which there are never longitudinal (azygos or hemiazygos) trunks lying parallel to the cardinals (figs. 8 and 10). Below these regions and above them on both sides there are to be found at some stage of ontogeny both sets of vessels, of which the cardinals disappear. But the uppermost supracardinal derivatives have no connection with the lower, except indirectly through the postcardinal stems in these regions which

act as common trunks for the respective inferior ascending supracardinal trunks and the adjacent cardinal trunks which will disappear. The walls of these common stems have existed before supracardinals have appeared; they exist after the rest of the lower postcardinal disappears; and no amount of azygos or hemiazygos labeling can disapprove the fact that they are postcardinal remains. These common stems are found in figures 4, 5, 16, and 17 of Sabin's account (7). In the first two figures just mentioned they are labeled postcardinal, and in the last two they are called azygos and hemiazygos. In case of the left side, I can find nothing in Sabin's figures to substantiate the claim that the only permanent connections of the azygos system to the cardinal system are those opposite the ducts of Cuvier. In all cases figured by Sabin, left supracardinal appears to unite with postcardinal well below the left duct of Cuvier. The conditions in the right side of Sabin's figures 5 (7) do not warrant a conclusion that there is a stage in which the right or the left 'ascending' supra- and postcardinal trunks are separated superiorly as far as the duct of Cuvier, nor do they warrant a conclusion that in figures 16 and 17 (7) the postcardinals have been 'dragged back' along the 'ascending hemiazygos.'

The apex of the angle formed by veins labeled *v.a.* and *v.c.p.* in Sabin's figure 5 (7) is not homologous with the apex of the angle between the vein in Sabin's figure 18 (*ibid.*) labeled *v.c.p.*, and the inferior continuation of the vein labeled *v.h.a.* In my experience the *v.a.* of Sabin's figure 5 is the right superior intercostal; if this be true, it would not be the 'short descending branch' of the azygos (7, p. 29); it could not be homologized with the 'ascending' branch in figure 17 of Sabin. If the *v.a.* of Sabin's figure 5 be 'ascending,' or azygos proper, where can the 'descending' branch of the azygos be found in the embryo under consideration? If it be a descending branch, then into what does it descend? What is its inferior relationship to the remainder of the supracardinal system?

In my experience, the upper part of the vein labeled *v.a.* in Sabin's figures 17 and 18 is the right postcardinal which normally degenerates to a very great extent. To it the term azygos

would be applicable in case only of abnormal persistence of the right postcardinal to form the azygos, the process being accompanied by the degeneration of the left duct of Cuvier; the term *vena azygos* is ordinarily not applicable to this portion of the postcardinal in the pig. The vein labeled *v.h.a.* in Sabin's figure 18 differs from any supracardinal derivative I have been able to find in any embryo. The degenerating left precardinal is ordinarily the only vein which at this time maintains its caliber in descending into this region. Ordinarily there is no occasion for cutting the superior supracardinal derivative in this region, since it does not emerge far from the body-wall. For instance, it was not cut in Sabin's figure 17 (7).

My results tend to show that the upper two to four segments of the left postcardinal vein enter into the formation of the hemiazygos. Variable amounts enter into the formation of the upper end of the azygos (as I have used the term azygos). Where an azygos parallels the upper part of the hemiazygos, this contribution of postcardinal may take place in two or more interspaces. The proximal end of the cervicothoracic vein may occasionally represent the uppermost portion of right postcardinal (figs. 1, 3, and 6).

Most of the confusion in Sabin's beautiful work results from a failure to distinguish between cardinal and supracardinal vessels. The labeling of a degenerating postcardinal as azygos is particularly unfortunate (7, fig. 18).

The later history of the right postcardinal is conspicuously absent in Sabin's work. The relationships of the upper regions of 'azygos' drainage of the right side are shown in no stage later than 22 mm. while on the left side they are figured no later than 28 mm. In the same way the history of the upper end of the left postcardinal is lacking in this same work on the fate of the posterior cardinals. In Sabin's fig. 9 (7), the upper end of the postcardinal receives small dorsal tributaries labeled hemiazygos. In fig. 16 (*ibid.*) I maintain this same postcardinal (here labeled by Sabin as hemiazygos) receives these same tributaries which are here unlabeled. There is nothing in Sabin's work to prove that the upper postcardinal of her fig. 9 degenerates. If it does so, the degenerative process should lend itself to investigation.

Extraordinary as it may seem, the cardinal system undergoes a most elaborate metamorphosis between the stages of 40 and 60 mm.

The work outlined was performed from 1913 to 1917 in Professor McClure's laboratory; I wish to acknowledge my deep indebtedness to Professor McClure for his help to me. The study was discontinued in 1917-18, but again taken up in 1919 in the laboratory from which it is contributed. A more complete article will appear later in which the argument employed will be primarily constructive.

CONCLUSIONS

1. The most superior portion of the hemiazygos of the pig is formed by the left duct of Cuvier and by two to five uppermost thoracic segments of the left postcardinal vein.

2. The right postcardinal vein enters into the formation of the azygos to whatever extent the azygos persists in those interspaces in which there is located embryonically a common stem of post- and supracardinal. On the right side this stem may run from the second to the eight thoracic interspace, but under conditions of greatest persistence of the azygos only the two or three inferiormost segments of the common stem are able to contribute to the azygos. The azygos may be practically absent.

3. The most superior portion of the right postcardinal persists as a small proximal part of the common trunk of the deep cervical, the posterior vertebral and the superior intercostal veins whenever the supracardinal anlagen of these veins have entered the right postcardinal below the right cardinocuvierian junction. For the common trunk of these veins the term cervicothoracic vein might be suggested.

4. The oblique vein of Kampmeier usually behaves in a manner described by him.

5. The permanent points of entrance of azygos and hemiazygos anlagen into the cardinal system are not at the level of the respective ducts of Cuvier, but from two to six thoracic segments below them.

6. There are no such things as descending branches of right and left azygos. The terminology for the azygos drainage of the pig needs no special simplification. On the right side the azygos (when it is present) is well separated from the right superior intercostal. On the left side the hemiazygos, when it is present, is well separated from the left superior intercostal. These separations take place in the region in which the sympathetic trunks cross the supracardinal lines. All four vessels are properly described as ascending.

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Un caso de persistencia de la vena cava superior izquierda en un
adulto de edad avanzada

En el presente trabajo se describe un caso de persistencia de la vena cava superior izquierda en un varón de setenta y nueve años de edad. Este vaso comunica con la vena cava superior derecha por medio de un pequeño vaso que presenta las relaciones que son comunes en la vena innominada izquierda. No existen comunicaciones con las venas pulmonares.

Translation by José F. Nonidez
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A CASE OF PERSISTENCE OF THE LEFT SUPERIOR VENA CAVA IN AN AGED ADULT

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ONE FIGURE

The persistence of the left superior vena cava is relatively common in still-born children, but its occurrence in the adult is rare enough to warrant a record of the cases. According to the table compiled by McCotter ('16), only ten cases of persistence of left superior vena cava with small anastomosis have been recorded for the adult. Ours is such a case and is of interest on account of the age of the individual in which it was observed.

The subject was a white male, seventy-nine years old, well developed and showed no marked signs of arterial sclerosis. The heart is normal in size and the external surface is well marked. No defects are present in the interatrial or inter-ventricular septa. The aorta and the inferior vena cava are normal and pursue their regular courses.

The external jugular veins are entirely absent. The right superior vena cava is formed by the junction of the subclavian and internal jugular veins. The left superior vena cava also is formed from the subclavian and internal jugular veins. At about 8 cm. above the base of the heart a small vein, homologous to the left innominate, runs obliquely across and connects the two cavae. There is no communication with the pulmonary veins. The left superior vena cava passes downward, terminating in the coronary sinus. In this part of its course it lies in the position usually occupied by the oblique vein of the left atrium (vein of Marshall), passing between the left pulmonary veins and the auricle of the left atrium. The enlarged coronary sinus empties as usual into the right atrium, below the valve of the inferior vena cava.

The azygos veins are very primitive, with no communication between the right and left veins. The right vein empties into the right superior vena cava at a point 3 cm. above the base of the heart. The upper intercostal veins on the right side form a large trunk and empty into the right vena azygos.

On the left side the azygos passes lateral and anterior to the aorta, and empties into the left superior vena cava 3.5 cm. above the base of the heart.

Grant ('17) has seen a case of double superior vena cava in the cat, in which, however, the coronary sinus had no communication with the right atrium, so that the coronary blood must have drained through the persistent left vena cava.

Smith ('16) describes a case of left superior vena cava without a corresponding right cava.

Our case is doubtless to be interpreted as the simple persistence of an early embryonic condition. Although the cross anastomosis between the two anterior cardinal veins was formed, the left anterior cardinal did not lose its connection with the common cardinal on the left side, as is normally the case.

The writers are grateful to Prof. Wayne J. Atwell for his suggestions and assistance in preparing this report.

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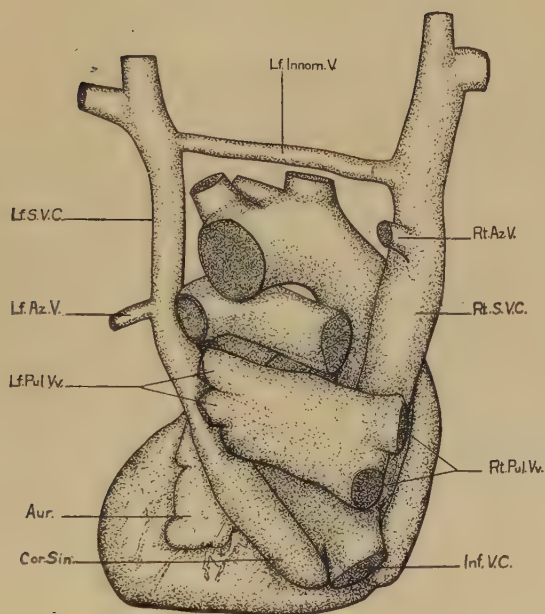


Fig. 1 Dorsal view of heart, showing course of great vessels. Two-fifths natural size.

Resumen por el autor, Joseph Hamilton Smith.
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Descripción de un caso de persistencia del conducto de Cuvier
izquierdo en el Hombre.

En el presente trabajo se describe un caso de persistencia del conducto de Cuvier izquierdo en un individuo humano adulto. Tres venas coronarias desembocan en una vena cardiaca común, que se reúne con un tallo longitudinal que desemboca en la vena subclavia izquierda. Este vaso venoso longitudinal representa porciones proximales persistentes de las venas pre- y postcardinales del feto. Sustituyen a las hemiazigos accesorias y las venas superiores intercostales de la anatomía del adulto normal, pero no tienen conexión alguna con las venas hemiazigos.

Translation by José F. Nonidez
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DESCRIPTION OF A CASE OF PERSISTENT LEFT DUCT OF CUVIER IN MAN

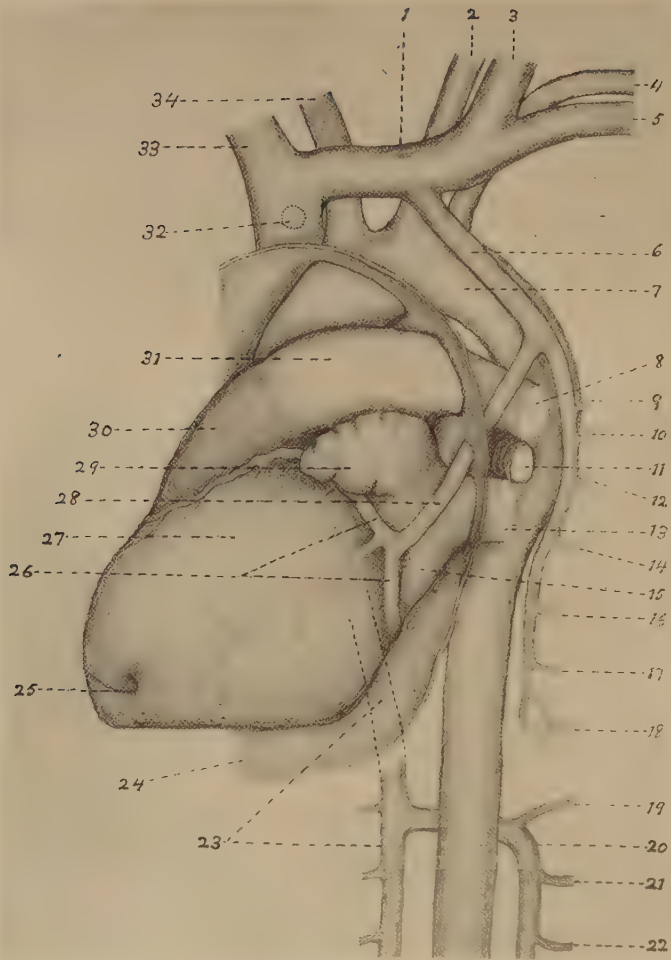
JOSEPH HAMILTON SMITH

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ONE FIGURE

The subject of this study was a colored male, approximately thirty years old. In addition to the chief vascular anomaly pertaining to a persistent left duct of Cuvier which drains through the left superior intercostal vein (persistent proximal portion of the left precardinal vein) into the left innominate vein, there occurs also an irregularity in the disposition of the left intercostal veins, and in the origin of the vertebral artery as a separate branch of the arch of the aorta just medial to the origin of the left subclavian artery.

The circumstance which led to the discovery of the persistent duct of Cuvier in this subject was the failure to find the orifice of the coronary sinus. Closer inspection of the heart after removal from the cadaver revealed a venous trunk leaving the pericardial sac in a fold of the parietal layer. This vessel is approximately the size of the normal coronary sinus, and is formed by the union of three smaller tributaries on the dorsal surface of the heart near the base of the left auricular appendage. Two of these tributaries approach the main trunk along the atrioventricular groove from opposite directions, while the third passes upward along the dorsal surface of the ventricular wall. The resulting common cardiac vein follows closely the usual path of the vestigial fold of Marshall, passing slightly anterior to the left primary bronchus and left pulmonary artery. Passing thence to a point just anterior to the arch of the aorta, the vessel there unites with the left superior intercostal vein to form a still larger trunk, which empties into the left innominate vein just medial to the division of this vein into left internal jugular



Drawing of heart and adjacent vessels, illustrating the anomaly of persistent left duct of Cuvier with proximal portions of the pre- and postcardinal veins. Two-thirds natural size. The apex of the heart is drawn upward toward the left. Drawing by Dr. Wilmer Baker.

1, left innominate vein; 2, left common carotid artery; 3, left internal jugular vein; 4, left subclavian artery; 5, left subclavian vein; 6, left superior intercostal vein (persistent proximal portion of left precardinal vein); 7, systemic aorta; 8, left pulmonary artery; 9, 10, 12, 14, 16, 17, 18, and 19, second to ninth left intercostal veins; 11, left bronchus; 13, left pulmonary vein; 15, left atrium; 20, hemiazygos vein; 21 and 22, tenth and eleventh left intercostal veins; 23, azygos vein; 24, pericardium; 25, hook in apex of heart; 26, coronary veins; 27, left ventricle; 28, oblique vein of left atrium, or Marshall's vein (persistent left duct of Cuvier); 29, left auricular appendage; 30, conus arteriosus; 31, pulmonary aorta; 32, point where azygos vein empties into the superior vena cava; 33, right innominate vein; 34, innominate artery.

and left subclavian, and almost immediately anterior to the point where the left common carotid arises from the arch of the aorta.

Normally, the proximal (cardiac) portion of the left duct of Cuvier forms the coronary sinus, while its distal portion, severed from the adjacent portions of the pre- and postcardinal veins, becomes impervious, and forms part of the vestigial fold of Marshall, a fibrous band extending from the left superior intercostal vein to the left atrium, where it becomes continuous with the oblique vein of Marshall which empties into the coronary sinus. Considered in the light of the normal course of events, the anomalous condition here described may be explained as the result of the persistence of the left duct of Cuvier and the related proximal ends of the pre- and postcardinal veins. That this vascular arrangement provided an efficient drainage system is clear from the otherwise apparently normal condition and the mature age of the subject.

As far as we have been able to ascertain, a similar anomaly of comparable degree has only been observed once previously. On pages 44 and 45 of the transactions of the Royal Academy of Science, Paris, 1738, occurs the following note: "M. Le Cat, Démonstrateur Royal et Chirurgen de l'Hôtel-Dieu de Rouen, a dit à L'Académie que dans un enfant de huit jours il avait trouvé les veines coronaires réunies dans un seul tronc qui sans pénétrer dans l'oreillette droite se jettait dans la veine sous-clavière gauche."

The accessory hemiazygos is presumably represented by the longitudinal stem caudad to the persistent cuvierian duct, the continuous left superior intercostal vein by the portion cephalad to the duct. No vascular connection can be discerned between the hemiazygos and the accessory hemiazygos veins.

This anomaly may have significance in relation to the question of the origin of the azygos system. The persistence of the embryonic vascular pattern as represented by a common cardiac vein which drains into a channel composed of the left superior intercostal and the accessory hemiazygos veins, without vascular connection with the azygos and hemiazygos veins, lends support to the view which denies direct participation of the postcardinal veins in the genesis of the azygos and hemiazygos veins.

Resumen por el autor, Wesley M. Baldwin.

La producción artificial de mónstruos de un tipo determinado por medio de los rayos X.

Al resumir brevemente los resultados del estudio de los ejemplares seccionados, uno de los más sorprendentes resultados obtenidos es la gran semejanza en los rasgos histológicos que presentan los embriones. La imagen microscópica patológica es prácticamente la misma en todos los ejemplares. El desarrollo anómalo de todos los esbozos, el estado de distensión exagerada de los espacios intercelulares, vasos y cavidades normales, las desviaciones citológicas que se mencionan a continuación y, finalmente, la presencia de núcleos expulsados de las células y masas protoplásmicas en las cavidades del cuerpo son pruebas suficientes de la acción nociva y uniforme de la energía acumulada en los rayos X. Los cambios citológicos están representados principalmente por variaciones en la morfología y tamaño de los núcleos, en el carácter del citoplasma y en la adquisición de contornos redondeados por parte de las células, y secundariamente por una diferenciación tardía, como puede verse en el adelgazamiento de las capas estratificadas y la reducción de las masas celulares. Todos los esbozos presentan estos rasgos generales, pero, como puede fácilmente suponerse, estos rasgos microscópicos aparecen más pronunciados y las desviaciones del tipo normal son más sorprendentes en el caso de aquellos sistemas en los cuales la diferenciación es normalmente más precoz, tales como los sistemas nervioso y vascular.

Translation by José F. Nonidez
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THE ARTIFICIAL PRODUCTION OF MONSTERS CONFORMING TO A DEFINITE TYPE BY MEANS OF X-RAYS

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TWENTY-ONE FIGURES

It has been recognized for some time that x-rays bring about injurious effects in the tissues and organs of the adult body and, as well, interfere with the progress of normal development in lower animals. The genetic deviations from normal have been obtained by raying either the fertilized ovum or the embryo at any stage of its developmental cycle. For the most part, the monsters produced by the latter method vary so greatly both in morphological detail and in histologic structure that attempts at analysis, either of the physical or chemical action of the rays or of the nature of the cytologic modifications which underly the abnormalities of tissues and organs produced, have failed to lead to definite conclusions. In the experiments to be presented here, however, the author has succeeded in producing a constant type of defect by means of a fixed amount of x-ray energy acting upon fertilized frogs' ova all of the same stage of development. In these experiments the external configuration and structural features of the specimens are identical. By reason, chiefly, of the standardized physical agent employed, as high as 96 per cent of the embryos utilized in any experiment present the same abnormal features.

During the past five years experimental work has been in progress comprising a study of the developmental results produced by exposing fertilized frogs' ova to different forms of physical energy such as ultra violet light rays, magnetism, electricity, and x-rays. In general the purpose of such experimentation has been to ascertain not merely the nature and mechanism

of production of embryological defects, but to gain a clearer insight, through a study of the abnormal, into the nature of the normal processes of differentiation and growth. This paper comprises but a small portion of that work, complete in itself, however, for the reasons mentioned above.

Repeated observation in this field of experimentation has revealed that protoplasmic changes in the cell-body are not histologically so readily demonstrable from the effects either of x-radiation or of radium emanations as are chromatin modifications in the nucleus. Deviations from type-mitotic figures have been observed frequently. Indeed, many experimenters have assigned to these nuclear changes the chief rôle in the causation of abnormal development, the manifest reason for which conclusion appears to be the existence of a line of least resistance in logical deduction. Adult tissues, on the other hand, show a variable degree of susceptibility to these two forms of physical energy. This susceptibility depends to a great extent upon the mitotic activity of the cells. Germ cells and developing blood cells are consequently readily affected by x-rays. Furthermore, embryonic tissues in general are more susceptible than the corresponding types in the adult.

Three outstanding facts which are possibly of significance have been observed in studies upon the effects both of x-radiation and of radium emanations. First, the effects are almost never seen immediately upon completion of the exposure, but always at some subsequent time. Secondly, the general effect of the energy upon developing embryos is to produce a gradual slowing-down of all of the processes of differentiation, leading, when the dosage is sufficiently great, to actual cessation and death. Lastly, there is a tendency toward the establishment in the rayed adult body of a chronic disease characterized by a sluggish repair process.

In a paper on "The Effects of Radium Emanations upon the Germ Cells and Fertilized Ovum of the Frog," O. Hertwig has presented a résumé of the biological results obtained in this field of experimental embryology. To this the author wishes to refer for a more complete detail of the results heretofore

obtained not alone with radium, but with x-ray energy as well. In brief, Hertwig ascertained that a shorter exposure to radium was sufficient to influence the fertilized ovum at the two-blastomere stage during the time of mitotic division than was necessary either immediately before or following this stage. The monsters produced by his radium method, both in external features and in microscopic detail, compare more or less closely with those produced by the author's x-ray method. Frequent reference will be made to these results in the course of this paper.

The source of x-ray energy utilized in these experiments was a special Coolidge air-cooled tube of a diameter of 7 cm., for the use of which the author is indebted and wishes hereby to acknowledge his sincere appreciation to the Research Laboratory of the General Electric Company at Schenectady. The tube had a capacity of 2.5 milliamperes at 35 kilovolts. The duration of exposure varied from two and a half to thirty minutes. The distance from the eggs to the target averaged 7 cm. The eggs used were those of the common green frog and bullfrog collected from ponds near Schenectady as soon after laying as was possible. Early experimentation demonstrated, first, that the jelly investing the eggs did not inhibit the action of the rays upon the eggs, nor, secondly, exert a deleterious after-effect upon them after the exposure, and, thirdly, that the position of the egg poles, animal or vegetable, with regard to the target, made no difference in the action of the rays, apparently, as evidenced by the developmental results obtained.

In a typical experiment, a group of from twenty to twenty-five eggs, retaining their jelly, were placed in a Syracuse watch-glass vertically under the target. No attempt was made to right the eggs so that the animal pole, for instance, of all of them would be uppermost. Three thicknesses of carbon-paper were next inserted between the target and the eggs to eliminate the influence of heat radiation. An exposure varying from two minutes and a half to thirty minutes was made under these conditions with a current strength of 1.8 to 2 mm. at 35 KV. The specimens were then transferred to a glass jar containing 1000 cc. of tap-water and permitted to develop, the water being changed daily.

Extracts from notes taken in the instance of several different experiments will be sufficient to give evidence of the constancy and uniformity of the type of monster produced as the result of this procedure. The first instance is that of the experiment of June 4, 1916. All of the eggs were in either a two- or four-cell stage. Fifty-three eggs were rayed. Eight died prematurely. The remaining forty-five demonstrated an anomalous condition, the external features of which were in the main identical. Twenty-five of these were sectioned for histologic study. Experiment D, June 14, 1916: Forty eggs were used in this experiment. Two died prematurely, thirty-eight presented the same type of abnormality. Six of these were sectioned. In experiment E of the same date, fifty-five eggs were used. One died prematurely, fifty-four were typically abnormal, and ten of these were sectioned. In the experiment of May 7, 1918, forty-seven eggs were used. None died prematurely. All forty-seven eggs showed the same characteristic deformity. Thirteen of these were sectioned. In the experiment of May 9, 1916, fifteen eggs were used. All developed abnormally.

These are, of course, isolated experiments and examples. The same results have been repeatedly and uniformly obtained in a total of many hundreds of eggs in work covering the past three summers. Where the two- and four-cell stage was utilized an exposure of 2.5 minutes was sufficient to produce the uniform abnormality. The figures illustrating this paper were made from the sectioned specimens referred to above.

All of the abnormal tadpoles conform to the type shown by figure 1, in the center of which there are two control normal tadpoles of the same age. These abnormal tadpoles are the results of one experiment selected at random from the whole series. The singular conformity of the abnormal tadpoles to a type of defect is one of the most striking features of the photograph. As is to be seen, the tadpoles are in general considerably reduced in length, breadth, and thickness. The head is remarkably dwarfed and, because of the developmental failure of the neck region, projects but little from the trunk. The usual prominences of the brain, of the suckers, and of the gill tufts are absent. But little can be seen of the eyes.

Hertwig has called attention to a stunted condition of the gill tufts in his radium embryos and also to the prevalence of corrugations, or wrinkles, of the epidermis noted upon the embryo in the region of the neck and head. The latter are to be observed as well in these x-ray embryos. A comparison should be made between these embryos and that represented by figure 3 of Hertwig's paper.

It is to be noted that the long axis of the trunk has suffered a greater proportionate loss than has either the breadth or thickness of the same. A marked dorsal concavity features this part of the embryo. It is accompanied by an increased ventral convexity which accentuates the normal bulging of the ventral wall of the trunk. A gross examination of the trunk revealed the fact, which was subsequently verified by the histologic sections, that this ventral bulging was owing in large part to the accumulation of fluid in the abdominal cavity. The abdominal parietes were so thin that the outline of the underlying and undeveloped yolk mass and intestines could be made out upon gross examination under strong transillumination. Hertwig had observed this same condition of the trunk in the radium embryos and referred it correctly to an hydropic condition. His figures 3, 4, and 5 demonstrate the same condition.

The tail possesses a marked downward bend which so alters the direction of its long axis that it meets the corresponding axis of the body at an angle instead of representing approximately the continuation of it. But little injury by the x-rays has been experienced by the tail; the length, breadth, and thickness of it have, relative to the corresponding diameters of the body, suffered, but, however, to a less degree. Both the dorsal and ventral fins show departures from normal in shape and in thickness. The presence of rounded elevations upon them give them an irregular and uneven contour. The differentiation of the myotomes, however, has progressed fairly normally, as might be inferred from the length of the tail. A lateral bulging in the dorsal fin at the point of junction of the tail with the trunk seems to be associated in a causal way with the ventral flexion of the tail. Reference to this feature will again be made. The irregu-

larity of the surfaces of the fins has been noted as well in the radium embryos.

The pigmentation in general of the embryos is normal and comparable to that of the normal controls. The activity of these embryos is, however, considerably reduced. For the most part, they lie on the bottom of the jar and only occasionally swim about. A greater agitation of the water was necessary to produce activity in them than was the case with the controls, and their swimming movements were feeble, in comparison, and spasmodic and soon subsided. Such as well has been seen with radium embryos.

No appreciable changes are observable in the external characters of either the x-ray or the radium embryos during the stages of development immediately following the raying. There is, however, a marked slowing-down of the developmental process. A latent period during which the external features, and microscopic as well, are normal intervenes before distinct morphological departures from normal make their appearance. Differentiation in these embryos has progressed, however, to a more advanced stage than one would suppose, judging from external features alone. The neural tube is closed; the optic cup and otic vesicle are formed; the enteron, great vessels, and kidney have all been differentiated, but all with certain pathological features, the significance of which will be pointed out later. The sectioned specimens demonstrate histologic changes which indicate a pathological condition of the cells of the anlagen. Such changes, however, make their appearance subsequent to the latent period mentioned above at a relatively late developmental stage.

Neither the morula nor the gastrula stages show variations from normal. In these stages both the animal and the vegetative cells are well differentiated. With the formation of the blastodermic vesicle (fig. 3), however, certain variations both in the character of the cells and the manner of their arrangement became pronounced. There is a marked tendency toward isolation of the cellular elements. This feature is not restricted to the cells of the animal half, but is found in the vegetative half as well. The intercellular spaces are relatively larger, however,

in the animal half of the egg than elsewhere. The tendency of the cells to assume a spherical shape, thereby fitting less closely to their neighbors, seems to be the chief cause for the increase in size of the intercellular spaces. But at this stage it is not possible to demonstrate either definite nuclear or protoplasmic changes. The blastodermic vesicle contains cell detritus or accumulations of protoplasm sometimes with a degenerated nucleus and oftentimes without. Later stages demonstrate the constantly increasing size of this mass of extruded cell substance.

Hertwig has called attention to the presence of a similar protoplasmic mass in like positions in the radium embryos. The author agrees with Hertwig in presuming that such protoplasmic and nuclear extrusions represent blastodermic substance which has been most seriously injured by the rays; that it has consequently lost its developmental function and, thus, relatively inert, has been extruded from the field of active differentiation into the cavity of the vesicle and into other hollow spaces of the embryo as these appear in later developmental stages. The assumption of a spherical shape on the part of the blastomeres with the consequent loss of extensive and intimate contact with neighboring cell borders is taken by the author as an indication of an injury to these cells and might be considered to represent the preliminary step to which the features just mentioned are the final step.

In no instance has the peculiar wrinkled appearance of the pigmented layer, observed by Hertwig and represented by him in figures 21, 22, 23, etc., been seen by the author as early as this stage. This wrinkling of the normally smooth pigmented layer of the egg occurs in the early stages before the total inclusion of the yolk mass. Some of these wrinkles assume the character of localized knotty or warty swellings. The absence of coordinated developmental tempo between the enveloping action of the ectoderm and the inclusion of the yolk mass, assuming these to be separate and independent developmental factors, would seem to underlie the formation of these folds; that is, a normal or excessive growth of the ectoderm with a delayed or normal inclusion of the yolk mass would upset the normal balance

between these two processes and produce a consequent wrinkling of the ectoderm. The author has produced this wrinkled condition in experiments where a greater amount of x-ray energy has been employed, but, as has been noted before, the standard dosage utilized in this present experiment failed to produce the condition at this stage. This feature helps to bear out the general contention that the greater the dosage acting upon the fertilized ovum the earlier in the developmental process deviations from the normal make their appearance.

Later stages (fig. 4) reveal extruded cells and masses of protoplasmic detritus in proportionally greater amounts. The spherical characters of both animal and vegetable cells are also well marked features. As subsequent developmental stages are followed, this mass of detritus becomes so great that a distinct stratum is formed and is readily demonstrable in the more dependent portions of the body cavities. The microscopic characters of this mass bespeak a vegetative and, as well, an animal-pole origin. The nuclei which appear in such masses are always smaller and more deeply pigmented than is the case with normal nuclei. Vacuolization of the cells now makes its appearance at the stage shown, the greater number of vacuoles being encountered more often in the yolk cells than in the dorsal region of the embryo.

In later stages (figs. 5 and 9), when the neural tube is well differentiated, it can be seen that the cells constituting this tube are small and have undergone a marked degree of isolation because of their spherical shape. The neurocele is relatively great in diameter and contains isolated, extruded cells, and cell detritus. Thus, early in the development of this system and long before the appearance of the nerve-fibre layer of the coele, unmistakable histologic appearances of degeneration are found. Where the injurious action of the rays is so uniformly distributed throughout the cells of the morula, as has been shown, it might be supposed that the anlagen first laid down would be the first to exhibit gross abnormalities. We might reasonably infer further that these abnormalities would become more and more pronounced through subsequent stages. The sectioned embryos

demonstrate such to be the case. The phenomena of cytological disorganization of the central nervous system are not restricted, however, to any portion or segment of that tube. Both the brain and the cord alike demonstrate the same relative degree of injury if due allowance be made for the normally precocious condition of the cephalic end of the tube.

As can be seen in the figures, at this stage the ectodermal and mesodermal layers have differentiated to a certain degree. The endoderm is more backward. Along the ventral surface of the embryo vacuolization and dissolution of the cell groups become more pronounced. Because of the abnormally large diameter of the enteron, the yolk mass seems relatively less prominent. Particular attention should be called to the close proximity of the neural tube to the ectoderm, which, as is to be seen better in sections of embryos of later stages (figs. 7 and 8), indicates a retardation of the normal recession of these anlagen from the ectoderm. As an additional feature of this phenomenon in much later stages the dorsal wall of the tube remains thin and imperfectly formed. The persistence through normally late stages of the neural ridges with the groove separating them, suggests a developmental step in the production of spina bifida, a condition which has not, however, been observed in the final stages of development of x-ray embryos, though frequently observed by Hertwig in his radium embryos.

But little tendency is demonstrated by the neuroblasts toward the formation of a fibrous layer in the cortex of the brain. In other words, stratification of the cerebral cortex is much delayed. Tracing the neural tube caudally, it is observed to recede more and more into the substance of the dorsal fin, away from intimate contact with the myomeres. As is seen in the photographs, this appearance is brought about as the result of an increase in the dorsoventral diameter with diminution of the lateral cross-diameter of the dorsal portion of the trunk. Later developmental stages of the neural tube show a certain relation between the amount of granular extruded protoplasm on the floor of the neurocele and the number of neuroblasts constituting its walls. For example, where this mass is greatest, the neurocele walls

are thinnest. The inference is clear. It would seem that this extruded matter represents degenerated and fragmented neuroblasts, and is an argument for the existence of definite cytologic changes produced in these cells by the x-ray energy.

In the later stages of development, as is shown by figures 13, 15, 16, 17, and 18, the brain wall gives few indications of definite stratification, the neurocele is both relatively and actually increased in diameter and the extruded mass of degenerated cell protoplasm and of nuclei in its interior is increased. The x-ray effects upon this system are of such a degree of severity and the retardation of differentiation so great that even in the latest stages the appearances of a normal tube are not assumed. In late stages the vesicle walls are often reduced to a single two-cell layer of small spherical neuroblasts. The external fiber layer is never more than imperfectly formed. Furthermore, the close association of the tube relative to the dorsal ectoderm is an unmistakable evidence of retarded development and is suggestive, as has been mentioned above, of spina bifida. There has not been seen, however, a splitting or doubling of the tube in these embryos, as mentioned by Hertwig.

In the region of the optic tract and bulbs in figure 10, 11, 13, 17, and 18, the cells composing the walls of both are irregular in outline and fail to conform to a definite stratified pattern such as is normal. Here again there is to be observed a spherical and isolated condition of cells. The ventricle of the brain (fig. 11) is still connected by means of the optic stalk with the optic cup. A portion of the cavity contains, however, detached, granular cell masses and nuclear material. In figures 13 and 18, representing later stages, evidences of cytologic disorganization, and a tendency toward spherulation are still apparent. No indication is given at any period of the formation of the secondary optic vesicle and no lens develops. A thin layer of mesoderm intervenes between the optic cup and the overlying epidermis. This layer does not appear to be the immediate cause of the failure of the lens.

Both Hertwig and Morgan, and, among others, the author as well, have noted effects from the use of sodium chloride solu-

tions upon developing embryos which are comparable, at least so far as the central nervous system is concerned, to the changes brought about by x-rays. In such specimens the neural tube walls are thin because of the retarded differentiation of the neuroblasts and, consequently, stratification in the walls of the neurocele is lacking. Columns and masses of rounded cell detritus appear in the brain vesicles as with x-ray embryos. This chemical produces also a stunting of the optic cup which consequently fails to approach the epidermis. The thick layer of mesoderm, intervening between the two, Hertwig concludes to be responsible for the failure of the lens to develop. In the x-ray embryos, on the other hand, the mesoderm intervening between the ectoderm and the optic cup is no thicker than is normally to be found. Failure of the lens to develop in these embryos would seem, consequently, to be referable to some other developmental factor.

The notochord differentiates early in development, as is shown by the various sections, and occupies its usual position ventral to the neural tube. In the trunk where the tube assumes a dorsal position with regard to the myomeres, as has been mentioned before, the notochord retains its position relative to it, but is as a result more dorsally placed than is normally the case. The diameter of the tube as revealed by cross-section is found to be both relatively and actually increased. The number of cells composing it, however, does not seem to be either much reduced or increased. An increase in size but not in number of the individual cells composing it appears to be the chief factor causing the increased diameter. This same feature is characteristic as well of the radium embryos and, as Hertwig has properly claimed, seems attributable to the condition of over-distention by fluid of the individual cell bodies. The cells constituting the cord, however, do not either assume a spherical form or retract their borders from their neighboring cells such as was observed in the neural tube. In no specimen is there an indication of a splitting or doubling of the cord.

The heart and great vessels require special attention. Hertwig has called attention to significant features in the appearance of

the heart tube in the radium embryos which he thinks to be correlated with the lowered vitality and sluggish movements of the embryos. Similar features of the x-ray embryos seem to bear out this point. The sections represented in figures 6, 13, 16, 17, and 18 which are to be compared to the normal show changes brought about by the rays in which both the cells and their arrangement to each other in this system are affected. The individual cells are undersized, more or less spherical in shape, and present a certain degree of irregularity in their arrangement. An estimation of the number of cells in cross-sections shows an actual reduction in number, while the presence of narrow spaces between the cell borders indicates a tendency toward retraction. The heart itself is reduced to a slender tube consisting of a thin, endothelial wall attached to the dorsal portion of the coelomic cavity by a dwarfed mesentery, the cells of which demonstrate the same individual characters as those of the heart wall.

The vessels leading off from the heart differ from the appearance of normal vessels both because of a great increase in diameter of their lumen and in the character and arrangement of their endothelial lining. Throughout the body all of the vessels are overdistended, though no trace of cellular blood elements is to be discerned in their interior. This contrasts sharply with the findings in radium embryos where numerous blood corpuscles fill up these vessels. While the large vessels in the x-ray embryos show no reduction in number, in other respects both the arterial and the venous systems demonstrate changes pointing back to the injurious action of the rays. Such are to be found in the reduction in number of the smaller vessels of the trunk and in cytologic changes in their walls similar to those mentioned above with the heart. The gill tufts of both the x-ray and the radium embryos are stunted and misshapen, the condition of which is very likely dependent upon, and gives proof of, the imperfection in development of the smaller vessels constituting their bulk. In the mesenchymal elements of their walls, as was mentioned, we find the same appearances of degeneration, of spherulation, and of isolation.

The pericardial cavity of the embryos presents relatively enormous proportions as can most readily be seen by a comparison of the normal in figure 20 with that of the abnormal in figure 16, 17, and 18. The slender endothelial tube representing the heart occupies, dorsally placed in the sac, but a relatively small portion of it. The endothelial cell lining is but partially complete and, moreover, these cells differ from normal both in shape and in arrangement. Aside from the common features of degeneration presented by them, in many instances the lining cells show a tendency to assume either a short columnar or cuboidal form. Still others, though in relatively less proportion, are spherical. It might be supposed that these morphological variations are indications of a tendency toward ultimate spherulation and consequent isolation from their neighbors. Some of the sections show the final stages of this process. At variable levels, clumps of these rounded endothelial derivatives are to be seen adhering to the endothelium proper by a slender cord of cells. In the more dependent portions of the sac cellular and nuclear detritus, observed before in connection with the neurocele, is to be found. The readiest explanation of its presence in this cavity is similar to that which was given in the former instance. The tendency of the cells both of the endothelial lining of the cavity and of the heart tube to become isolated through spherulation together with the general resemblances to these cells by the extruded cells seems to be evidence sufficient of their true origin.

In none of the embryos has the heart tube differentiated into a muscular layer. It is difficult to understand, consequently, how the circulation could have been maintained by so defective a tube. The circulation could not have been other than in a condition of complete or incomplete stasis. This being true, the condition of sluggish motility of the tadpoles finds at least partial explanation.

Attention has been called to the presence in both radium embryos and in these embryos of certain ectodermal wrinkles or folds which are more frequently observed in the neck and the caudal trunk areas. They are significantly absent from the area of the trunk occupied by the pericardial sac. The reason

for their absence in this area appears to have a mechanical basis. Where the trunk is overdistended through the accumulation of fluid, as this area, for example, the epithelial folds are necessarily flattened out, but where the underlying parts have been so affected by the x-rays as to be stunted or dwarfed, the epithelium, suffering less in the proliferation of its cellular elements, is necessarily thrown into folds in order to accommodate itself to the limited surface area.

The epidermal cells show a tendency toward irregularity in size and in arrangement. The formation of a stratified layer is consequently only imperfectly effected. An inequality in thickness of this layer results, and where this is most marked, as the neck or caudal trunk areas, very frequently a condition of vacuolization of the cells together with an actual tunneling by small spaces of the cell masses can be seen. The presence of these wrinkles and localized epidermal thickenings accounts in part at least for the irregularities in outline and in diameter of both the dorsal and the ventral fins of the embryos. As has been mentioned before, these are considerably broader and more bluntly formed than normal. The entire cause for this abnormal appearance cannot be referred entirely, however, to the epidermal features. The sectioned embryos demonstrate the presence of overdistended vascular channels in the mesenchymal base of the fins and enlarged intercellular spaces as well. The prominent ventral inclination of the tail appears to be caused chiefly by this means, the vessels concerned lying in the base of the dorsal fin at the junction of the tail with the trunk.

The ear vesicle, considered normal in radium embryos, presents unmistakable evidence of pathological changes in the x-ray specimens. The overdistention of it is not relatively so great as is the case with the neurocele and the pericardial cavity. The amount of detritus in the more dependent portions of the vesicle, however, is, as one might reasonably infer, proportionately less, inasmuch as the number of cells surrounding this cavity from which this material seems to be drawn is relatively less. To the features of normal differentiation of the vesicle cells, the phenomena of pathological change in these cells bear an identical

inverse ratio to that noted in the nervous system and in the vascular system.

Hertwig has called attention to the close relationship of the blastodermic vesicle to the developing enteron. The floor of the latter is composed frequently of a thin, single layer of cells which occasionally may break through, thus affording a direct communication between the vesicle and the cavity of the enteron. These features, though first noted by Hertwig in the radium embryos, have been observed as well in the x-ray embryos. The cells of the enteron are apparently quite susceptible to the action of x-rays. Abnormalities both in structure and in arrangement make their appearance early in the development of this system. These show, as was true of the nervous system, a progressive tendency toward more marked abnormality as development advances. The pharynx, though undersized and abnormal as regards its cellular characters, preserves its normal relationship to the brain and to the heart. The gill pouches are, however, usually deficient in number and underdeveloped in size. Again attention must be called in this connection to histological features of the dwarfed external gills. The changes producing the stunted condition seems to point to certain deficiencies in the development of the vascular tufts which normally make up the bulk of these gills. In the instance of the former, however, the cells constituting the lining endothelium are, because of their pathological character, brought about by the x-rays, the apparent cause of the defective development of the pouches.

One of the most characteristic features of the head region of these embryos (fig. 1.) is the undersize of the snout. The defective development of the mouth and pharynx revealed by cross-sections is undoubtedly correlated with this appearance of the snout. Caudal to the pharynx, the enteron demonstrates a lagging tendency of the tube cells to differentiate. In the liver, pancreas, stomach, and the intestines differentiation begins relatively late, and in the instance of the former two viscera was never quite complete at the time when the embryos were killed. In all, however, the cytologic characters are those which have been seen in the pharynx, in the neural tube, and in the

heart; degeneration, spherulation, and isolation. As might be readily inferred from the great number of cells lining the enteron and the ducts of its adnexa, the actual amount of protoplasmic and nuclear detritus is proportionally great in comparison with that of the systems before mentioned. In many specimens, the process of extrusion of pathological nuclei and of cell masses has taken place to such an extent that relatively large clumps of this detritus are to be found throughout almost the entire length of the enteron.

The condition of the myomeres is well shown by figures 2, 6, 7, 8, 12, 15, and 19, in cross-section, and in longitudinal section by figure 14. There does not appear to be a reduction in their number, but a lagging tendency toward differentiation is demonstrable. Irregularities in shape, granulation of the cytoplasm, and the inclination toward spherical cell outlines are the characteristic cytologic characters. The belated differentiation of muscle fibrils is very likely one of the factors, in addition to the cardiac abnormalities noted before, accounting for the sluggish behavior and feeble motility of the tadpoles.

Features parallel to these are to be noted also in the mesenchymal cells immediately adjacent to the myomeres and elsewhere in the body and tail of the embryo. The gross structural defects here and in the muscular system are not so evident naturally as those observed in the nervous system because of the normally antecedent period of differentiation of the latter. The presence of these cytologic characters is taken by the author, however, as evidence of the susceptibility of the cells of this form of tissue to the action of x-rays, while proof that they are less susceptible is lacking. Among the cell masses there are many individual cells to be found whose outline and nuclear features give unmistakable evidence, as has been referred to as well in the radium embryos, of an effort on the part of the masses toward extrusion of these pathological elements.

A distinction may be drawn at this point between the effects of x-rays and of radium. Hertwig had observed certain departures from normal in the neural tube paralleling those found in the x-ray embryos, but the degenerative changes noted in the

remaining systems of the embryos are not so prominent a feature in the radium embryos. As might readily be inferred, a varying reaction upon the part of the embryo anlagen is brought about through these two physical agencies. The x-ray effect bespeaks a generalized abnormality affecting all of the cells at this stage of development, whereas radium emanations seem to bring about their greatest effect in the central nervous system.

It is remarkable that cytologic variations should be most apparent in the relatively large and late-differentiating yolk mass (figs. 3, 4, 5, and 9). Upon a morphological as well as a staining reaction, it is possible to determine the outlines of the liver, spleen, and pancreas in this cellular mass at this stage in the controls (fig. 21). Differentiation and growth among these cells are so belated in the rayed embryos (figs. 2, 8, 12, 15, and 19), however, that the typical organ shape is not assumed. In the large mass of yolk cells there appear many small isolated pyknotic nuclei invested with a limited amount of protoplasm and also occasional masses of degenerated granular protoplasm of variable size and containing no nuclei. Hertwig looks upon the presence of these nuclear and protoplasmic masses as indications of extrusion because of their pathological features. Their presence in the x-ray embryos may be taken to indicate, moreover, a variable degree of susceptibility to the rays since the cells are not all affected alike.

The general appearance of the pronephric tubules, as is to be seen in figure 15, is comparable to some extent to that of the ear vesicle. The lining cells are characterized by the same pathological features noted before in the vesicles. The lumen of the tubules is overdistended and contains masses of extruded cells and of protoplasm. In the radium embryos, on the contrary, this organ and the Wolffian duct are well developed, but the tubules of the former are overdistended with blood corpuscles. The corpuscles are absent in the x-ray embryos.

The large size of the cephalic portion of the celomic cavity has been referred to. Figures 6, 13, 16, 17, and 18 demonstrate especially well the pericardial portion of it. At some levels the yolk mass is restricted to the median portion of it (fig. 19).

The lining membrane is incomplete, the cells are irregular in shape and in size and demonstrate pronounced pathological changes. The dependent portions of the cavity are filled with both cellular and nuclear detritus. The cavity itself contains during life a clear fluid which is very likely lymph, the presence of which, as Hertwig has contended, is undoubtedly correlated with the overdistended condition of the blood-vessels and the imperfect development of the heart and probably indicates stasis of the blood-stream.

In briefly summarizing the results of the study of the sectioned specimens, one of the most striking facts elicited is the great similarity of the histologic features presented by the embryos. The microscopic pathological picture is practically the same in all of the specimens. The anomalous development of all of the anlagen, the overdistended condition of intercellular spaces, of vessels, and of normal cavities, the cytologic deviations referred to, and, lastly, the presence of extruded nuclei and of protoplasmic masses in the body cavities are sufficient evidence of the injurious and uniform effect of x-ray energy. The cytologic changes are expressed primarily by variations in the morphology and size of the nuclei, in the character of the cytoplasm, and in the assumption of spherical outlines by these cells, and secondarily by retarded differentiation, as is to be seen in the thinning of stratified layers and the reduction of cell masses. All anlagen demonstrate these general features, but, as might readily be supposed, these microscopic features are most pronounced and the gross deviations from normal most striking in the instance of those systems in which differentiation is normally most precocious, such as the nervous system and the vascular system.

The identity of histologic changes seen in the various systems argues strongly against the conclusion that the normally first differentiating anlagen are either especially susceptible to the activity of the rays or have been the most markedly affected. The evidence gathered from a close cytologic study of other anlagen later to develop justifies the conclusion that their cells have been likewise affected and apparently to the same degree. The question does not seem debatable that the fundamental

changes brought about by the x-rays are very likely to be found in the structure of the individual cells of the anlagen. The gross deviations from normal become, consequently, more and more pronounced as the affected cells enter upon more and more advanced steps in the differentiation of their anlagen. Naturally, where the life of the embryo is terminated before all of the anlagen have completed their differentiation, gross defects are less conspicuous in those developmentally incomplete. In the instance of such as these histologic characters are more to be relied upon than macroscopic departures from normal. These are fully comparable to the evident abnormalities of cells of the affected more precocious anlagen when comparison is made at corresponding stages of differentiation.

It may be well to add parenthetically at this point observations which have been made upon embryos subjected to varying amounts of x-ray energy. When the amount used is greater than the dosage given in this experiment, the embryo dies earlier and demonstrates both a gross and a microscopic disorganization of the central nervous system, but with the other systems, such as vascular and digestive, in an undifferentiated condition. When the dosage given is somewhat less in amount than this, the embryo lives long enough to present a pathological picture of the same essential abnormal characters in both the nervous and the vascular systems, but with the remaining tissues undifferentiated. In still other instances, where the dosage given is a little greater than the standard dosage used for this experiment, more and more of the systems come into definition, because of the longer life of the embryo, and present the same abnormal gross and microscopic characters; and in those final instances where the x-ray dosage is small enough not to cause the rapid premature death of the embryo, but permits the viability of the embryos to last long enough for the differentiation of all of the body systems, these same gross and microscopic features are then characteristic of all of the systems. Further consideration of this aspect of x-ray experimentation will be deferred, however, to another paper.

We may, accordingly, briefly summarize the more significant features seen in this experiment as the effect of x-ray energy upon developing tadpole embryos: 1) No histologic or morphological changes are at once discerned in the rayed embryos. The embryos experimented upon have at first every external appearance of the control specimens. The developmental end-results bespeak, however, a histologic alteration with possibly an antecedent chemical modification in the blastomeres of the two- or four-cell stage. 2) Morphological changes, both gross and microscopic, appear first only after a certain time interval has elapsed. The duration of this interval is predetermined in an inverse ratio by the amount of the dosage. 3) The first demonstrable gross variation from normal is a general slowing-down of the developmental process, such as is expressed by a retardation of the closure of the blastopore, by the belated formation of the neural tube, and by the slowness of elongation of the embryo. 4) That all tissues of the embryo are affected is denoted by the pathological appearances of the cells and of the nuclei, by the presence of nuclear and of cytoplasmic extrusions, and by the defective morphology of their organs. As corollary to this statement may be added the observations that the embryo possesses a progressive tendency toward an increasingly abnormal development up to a degree determined by the viability of the embryo. Consequently, a constant and uniform type of deformity is produced through the utilization of a fixed amount of x-ray energy. There are no gross or microscopic departures from this type.

Before attempting to consider the probable nature of the physical and chemical changes brought about in the embryo by this form of energy, it may be well to survey briefly the literature on the general subject of the effects of x-rays on the developing embryo and adult body tissues. The biological effects of x-rays have been studied by a number of investigators whose work has been frequently referred to in the general field of experimentation, and the author consequently finds it not necessary to make more than passing mention of the results of their investigations. The character of the changes brought and the nature

and specificity of the cytologic variations and also the gross structural reactions to this form of energy have been considered by Mueller, Petry, Ghilarducci, Milani, Haerberstaedter, Unzeitig, Cuillemont, Szilard, Degrais, Kroenig, Walther, Cardinale, Eckstein, Eden, Murphy, Richardson, Bordier, Lopriori, Galimard, and Gaskell, among others. The observations of these men go a great way toward associating the specificity of tissue reaction to the selective absorption of x-ray energy. The demonstration of a stimulating effect upon growth and upon differentiation of tissues both in plants and in animals has been given by Schwarz, Lengellner, Colm, Foersterling, Kruhenberg, Hastings, Runner, Gilman and Baetjer, Haecker, and Lebedinsky. One of the most recent and most thorough studies on this question of the stimulating dosage necessary for the prolongation of life among invertebrates is that of Davey upon *Tribolium confusum*. Pfeiffer with Schwimmermacher, and Maldiney with Thouvenin succeeded in increasing the germinability of seeds, while Menertrier and Mallet, Rowntree, Benjamin, Ruess, Slenka and Schwartz, Promsy and Drevon, Gilman and Baetjer, Haecker and Lebedinsky, Aubertin and Beaujard, Murphy and Norton succeeded in accelerating growth. The condition of sterility in the silkworm, in rats, in guinea-pigs, in cats, and in dogs, brought about through the influence of x-rays, has been studied by Regaud and Nogier, Trillwich, Barratt and Arnold, Hastings, Beckton and Wedd, Seldin, Bergonie, Tribondeau, Fraenkel, Regaud and Dubreuil. Bardeen, moreover, observed that the phenomenon of regeneration of lost parts in lower animals is lost after exposure to x-rays. The results of Lecercle's experiments, where, upon raying the hind quarters of rabbits, there is a lowering of the rectal temperature for one and one-half hours afterward, are difficult of interpretation.

It has been recognized, moreover, that x-ray energy will produce definite changes in certain chemical substances. A lowering of the iodine number of olive oil has been observed by Duste, while a precipitation of the same element from chloroform solutions has been observed by Bordier and Galimard. Starch has been transformed to dextrin (Colwell and Russ).

Certain dehydrating effects upon chemical compounds have been observed by Bordier and Galimard. Werner studied the reaction of these rays with cholin. Solutions have been altered in chemical constitution (Schwartz), while the effects of radiation on fermentation and on enzymes have been studied in connection with substances such as must, wine, vinegar, alcohol, butter, milk, eggs, and other agricultural products (Bruttinin and Richards).

As related to cellular activity and the phenomena of mitosis, the work of Lepine and Boulud commands attention. These investigators determined that x-rays increased the glycolytic power of the cells. The mitotic activity of the cells was observed to be reduced by Gaskell; in *Ascaris*, Perthes noted it to be delayed, while the activity of protoplasmic movement was found by Seckt and Lopriore to be increased, but, on the other hand, restrained through an increase in the dosage (Lopriore). A number of other investigators have recorded pathological cellular conditions, the major interest being centered in observations upon the various phenomena of chromatin alterations (Clumet, Scholtz, and others).

Summarizing the facts having a biological significance, but at the same time allowing that those results are not all dependent directly upon x-ray energy for their cause, we find, first, that the mitotic process may be either accelerated, retarded, or made abnormal; secondly, evidence has been adduced which points to a susceptibility to the rays not alone of chromatin, but of cytoplasm as well; thirdly, the phenomena of differentiation and of growth may be accelerated, retarded, or rendered abnormal; fourthly, a decidedly selective action of the rays has been demonstrated by studies on adult types of tissues, and, lastly, definite changes of a chemical nature both in the protoplasmic content of cell bodies and, more specifically, in enzymes may be produced by x-ray energy.

Positive experimental evidence at present points to a definite chemical reaction which, it is not difficult to prove in the two- and four-celled ova, must be of intracellular character. This is contrary to the biological hypothesis of Hertwig. In this

author's experiments the evidence of protoplasmic reaction is demonstrated by numerous masses of extruded detritus could be only with difficulty referred solely to chromatin reactions. To go still further in this criticism, the chief argument against the acceptance of the biological hypothesis is its inadequacy in accounting for the non-nucleated protoplasmic detritus. Furthermore, his objection to Schwartz's lecithin-alteration contention, on the ground that the division and subsequent distribution to the blastomeres of this modified lecithin content of the ovum should occasion abnormalities of maximum effect during the earlier stages the very reverse of the cumulative effect observed, does not appear valid as an hypothesis in the light of modern genetic cytochemistry, according to which the very reverse should be expected, as is verified by the present experiments.

We have not as yet identified the character of the chemical change effected and much less the kind of substance influenced, whether protein, lipin, or carbohydrate, but, inasmuch as the developmental end result both gross and microscopic is identical in every instance, we may reasonably assume that the chemical change brought about by the x-ray energy is definite and the same in the numerous specimens. Furthermore, it is more in conformity with modern chemical ontogenetic views to assume that the pathological cytologic features characteristic of all the tissues are directly referable to the distribution to these cells of the abnormal chemical constituents. Experiments of this nature in which the defect is uniform mark, therefore, a preliminary but essential step in the chemical identification of the change experimentally induced.

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PLATE 1

EXPLANATION OF FIGURES

1 A photograph of embryos rayed June 5, 1918, 50 milliamperes at 50 KV. for a period of 2 minutes and 20 seconds at 17 cm. from the target. Fifty-five eggs were used for the experiment. All show the same gross defects. Two have, in addition, a lateral flexure of the trunk. The most marked external features are the retarded growth and reduced axes of the trunk, the dwarfed head, the ventral distention of the trunk, and the flexure of the tail. In the center of the photograph two normal control tadpoles have been inserted.

2 A photograph of a section through the trunk caudal to the position of the heart. The yolk mass with the contained enteron shows no indications of a differentiating liver or pancreas. The coelomic cavity surrounding it is enormously distended. The notochord is composed of distended cells, while dorsal lies the neural tube with the broad and prominent dorsal fin. The cells composing the myomeres are spherical and the intercellular spaces are relatively large. Tubules of the pronephros in a distended condition are to be noted in the mesenchymal tissue lateral to the dorsal portion of the coelomic cavity.

3 A section through an egg early in development showing the blastocele. The spherical character of the cells with the relatively large intercellular spaces are characteristic features of this stage.

4 A later stage than figure 3 in which are shown the combined cavities of enteron and blastocele (p. 20) containing extruded cells and cell detritus. The neural groove persists. A thickening of the ectodermal layer with vacuolization, spherulation, and isolation of the yolk cells are characteristic of this stage.

5 and 9 These figures represent stages later than that of figure 4. In these the neural tube has separated from the ectoderm. A vacuolated appearance of the notochord cells of figure 9 is apparent. Spherulation and isolation of the cellular elements of the yolk region are prominent features.

6 This photograph shows a cross-section through the embryo at the level of the heart. The overdistended pericardial cavity with its irregular lining cells contains extruded cells and cell detritus. The heart tube occupies but a small portion of the cavity. The enteron is relatively large with the distended notochord and brain dorsal to it. In the neurocele extruded cells and protoplasmic detritus are to be seen. The spherular and isolated character of the mesodermal cells are evidences of x-ray injury. The ectoderm evidences by irregularity in thickness after effects from the same cause.

7 In this photograph the primitive layers are well differentiated. The cells of the neural tube are still continuous with those of the ectoderm. Special attention is directed to the irregularity in thickness of the ectoderm. Cellular debris is to be noted in the enteron.

8 In this figure the vacuolization and distended condition of the notochordal cells and the dorsal location of the neural tube in the dorsal fin are to be noted.

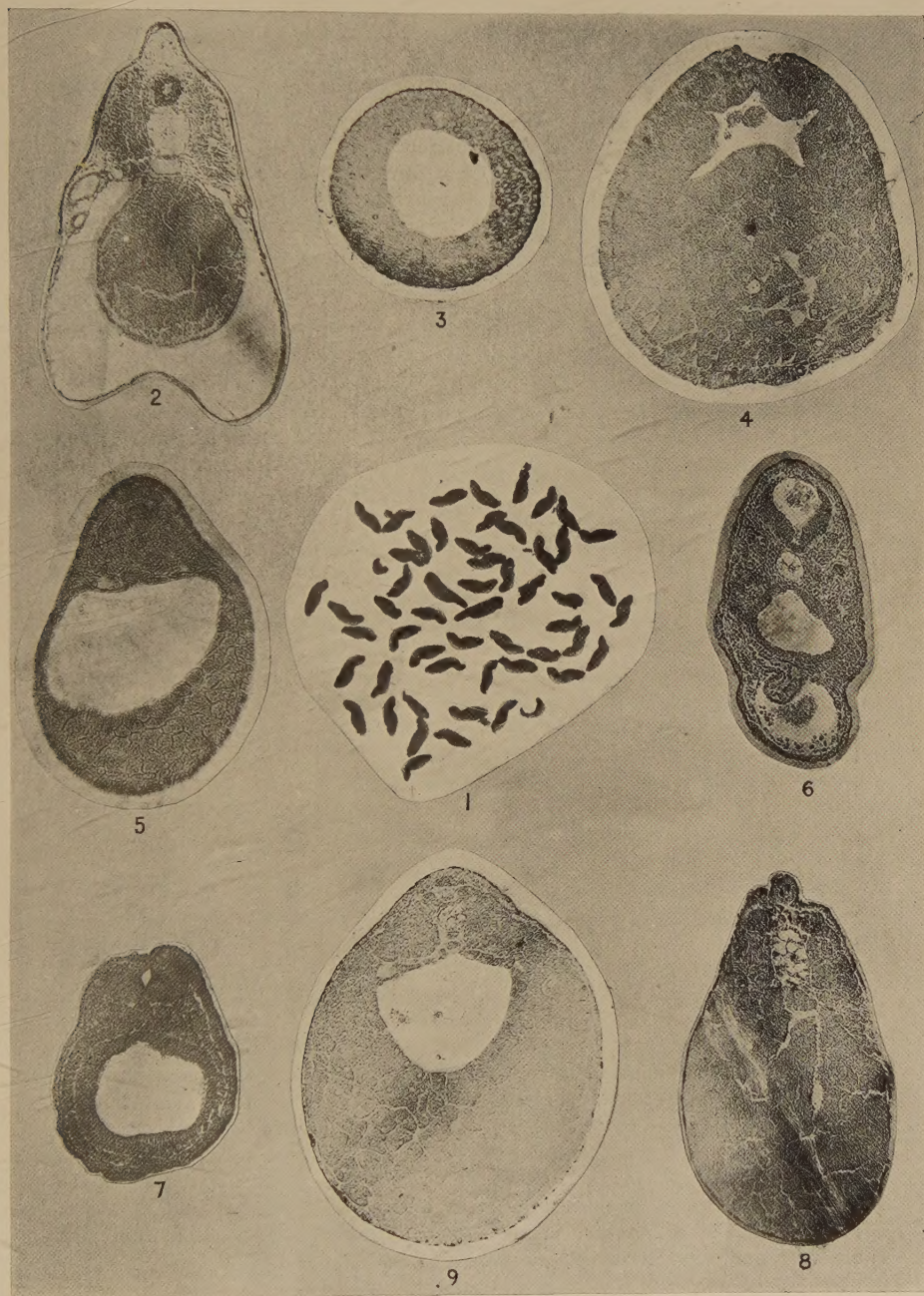


PLATE 2

EXPLANATION OF FIGURES

10 and 11 In these photographs the section knife passed through the brain at the level of the optic stalk. Stratification of the vesicle walls has not yet appeared. In neither photograph is there an indication of lens formation as yet, but a thin layer of mesodermal tissue separated the bulb from the ectoderm. Cell detritus is to be noted in the vesicle in figure 11. The isolated condition of the mesodermal cells of figure 10 is quite apparent.

12 This photograph was taken from a cross-section through the yolk mass. Upon the left, irregularity in thickness of the ectodermal layer is apparent. The dorsal fin is prominent as are also the overdistended cells of the notochord and the relatively large coelomic cavity.

13 This photograph shows the heart tube lying in the large pericardial cavity. Irregularities in shape, in size, and in arrangement of the cells composing the heart tube are prominent features. In these embryos this organ does not differentiate further, which condition accounts in part, at least, for the sluggish behavior of the tadpoles. The brain cavity is almost completely filled with cellular and nuclear detritus. Its walls give no indications of stratification, but, on the contrary, demonstrate the same features of disorganization as were noted in the heart tube. To either side of the ventral portion of it the optic vesicles are to be seen featuring the same irregularities in their constricted cells. No indication of a thickening of the overlying ectoderm with lens formation can be made out. Spherulation and isolation of the mesodermal cells are readily seen.

14 A longitudinal section through the trunk and tail of an x-rayed embryo. The notochord flanked by the myomeres is to be noted.

15 This photograph shows especially well the wrinkles noted in the ectoderm.

16 to 18 These photographs show the disorganized condition of the brain vesicle, of the ectodermal cells overlying it, and of the heart tube, with its mesenterly and the relatively enormous size of the pericardial cavity. Cellular detritus is to be made out in both the latter, the enteron, and the ear vesicle. The disarranged condition of their lining cells is also prominent, as well as the abnormal condition of the mesodermal tissue. These features are to be noted especially well in figure 18.

17 In this photograph the overdistended brain vesicle is almost completely filled with cell detritus, the amount of which balances the loss in thickness of its walls. The cells of the latter show no attempt at stratification. To the left the stunted optic stalk with its vesicle projects toward the ectoderm, the cup and lens being absent, however. The irregularities of the endodermal cells of the enteron are apparent. There is no attempt at orderly arrangement. The heart and pericardial features are comparable to those of figures 16 and 18.

19 While this photograph shows the same features of ectoderm and mesoderm, neural tube and notochord, its most prominent feature is the undifferentiated yolk mass and retarded enteron in the enormously distended coelom.

20 and 21 These are photographs of normal embryos, the section represented by figure 20 being taken at the level of the heart and the other at the level of the liver and pancreas. The former photograph is to be compared with figures 6, 13, 16, 17, and 18, which were taken from x-ray embryos at approximately the same level, and the latter with figures 2, 12, 15, and 19.

